PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
SMK/BP5859293		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/02197	07/06/2000	07/06/1999
Applicant		
THE UNIVERSITY COURT OF THE UNIVERSITY OF ABERDEEN		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

PEPTIDE HAVING FOR FIBRINOGEN FRAGMENT E ACTIVITY, ANALOGS, ANTIBODIES AND USES THEREOF

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 12

Present claim 2 relates to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the compounds of claim 1 and fragments and variants thereof which have common structural features. Variants of fragments of the peptides of claim 1 are not covered by search because this would include compounds having no structural features common to those peptides of claim 1.

Present claim 12 relates to a product defined by reference to a desirable characteristic or property, namely being active in a identifcation process of claim 8.
The claims cover all products having this characteristic or property, whereas the application does not provide support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for claim 12.

The objections raised for the claims 2 and 12 also apply to dependent compound claims and to those independent claims using, employing and referring to the compounds mentioned above

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02197

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K7/08 C07K16/44 C12N5/12 C12N15/11 C12N15/62
C12N15/63 G01N33/68 A61K38/10 A61P9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, STRAND, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 605 797 A (BEHRINGWERKE AG) 13 July 1994 (1994-07-13) page 5, line 6 - line 7; claims; examples	1
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1992 THOMPSON W D ET AL: "Angiogenic activity of fibrin degradation products is located in fibrin fragment E." Database accession no. PREV199395013436 XP002152690 abstract & JOURNAL OF PATHOLOGY, vol. 168, no. 1, 1992, pages 47-53, ISSN: 0022-3417	1,19

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2000	28/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuhr, C

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1993 STIRK C M ET AL: "Presence of growth-stimulating fibrin degradation products containing fragment E in human atherosclerotic plaques." Database accession no. PREV199497070046 XP002152691 abstract & ATHEROSCLEROSIS, vol. 103, no. 2, 1993, pages 159-169, ISSN: 0021-9150 -----	1,6,19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/02197

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0605797 A	13-07-1994	DE 4242736 A	23-06-1994
		AT 177758 T	15-04-1999
		AU 676859 B	27-03-1997
		AU 5243593 A	30-06-1994
		CA 2111645 A	18-06-1994
		DE 59309458 D	22-04-1999
		ES 2129487 T	16-06-1999
		JP 6256388 A	13-09-1994
		US 5599678 A	04-02-1997
		US 5981697 A	09-11-1999

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 February 2001 (12.02.01)	
International application No. PCT/GB00/02197	**Applicant's or agent's file reference** SMK/BP5859293
International filing date (day/month/year) 07 June 2000 (07.06.00)	**Priority date** (day/month/year) 07 June 1999 (07.06.99)
Applicant MELVIN, William, Thomas et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

27 December 2000 (27.12.00)

[ ] *in a notice effecting later election filed with the International Bureau on:*

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

KREMER, Simon, M.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

Date of mailing (day/month/year)
15 August 2000 (15.08.00)

Applicant's or agent's file reference
SMK/BP5859293

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/02197

International filing date (day/month/year)
07 June 2000 (07.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [X] the nationality [X] the residence

Name and Address
THE UNIVERSITY COURT OF THE
UNIVERSITY OF ABERDEEN
Regent Walk
Aberdeen AB24 3FX
United Kingdom

State of Nationality: GB | State of Residence: GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:
New applicant for all designatd states except the US. MELVIN W., THOMPSON W. and STIRK C should now be listed as applicants/inventors for US only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
I. Britel

Telephone No.: (41-22) 338.83.38

WO 00/75175
PCT/GB00/02197

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
KREMER, Simon, M.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

RECEIVED
21 DEC 2000

Date of mailing (day/month/year) 14 December 2000 (14.12.00)	
Applicant's or agent's file reference SMK/BP5859293	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/GB00/02197	07 June 2000 (07.06.00)	07 June 1999 (07.06.99)

Applicant
THE UNIVERSITY COURT OF THE UNIVERSITY OF ABERDEEN et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AG,AU,DZ,KP,KR,MZ,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,
   GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,
   NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   14 December 2000 (14.12.00) under No. WO 00/75175

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Col mbettes
1211 G n va 20, Switz rland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

14

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SMK/BP5859293		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02197	07/06/2000	07/06/1999
International Patent Classification (IPC) or national classification and IPC C07K7/08		
Applicant THE UNIVERSITY COURT OF THE UNIVERSITY OF ABERDEEN		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/12/2000	10.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Jenn, T Telephone No. +49 89 2399 7348

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02197

I. Basis f th r p rt

1. With regard to the **l ments** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-3,5-8,10, 12-48	as originally filed	
4	with telefax of	12/07/2001
9,11	with telefax of	18/07/2001

Claims, No.:

1-29	with telefax of	12/07/2001

Drawings, sheets:

1/3-3/3	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 19,21-23,25,26.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 19,21-23,25,26.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.
   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;

citati ns and xplanati ns supp rting such stat ment

1. Statement

Novelty (N)	Yes:	Claims	1-18,20,24,27-29
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-18,20,24,27-29
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-18,20,24,27-29
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

R It m I

Basis of th r port

The subject-matter of claims 21-23, 25 and 26, all in part (excluding their dependance on claim 19) is not anticipated or suggested by the available prior art documents and can therefore be considered as new and inventive.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question whether the claimed invention appears to be novel, to involve an inventive step or to be industrially applicable have not been and will not be examined for the subject-matter of **claim 19**, because no international search report has been established for the modulator of said claim 19 (See the International Search Report; Obs: Claims have been amended, and the amended claim 19 corresponds to the original claim 12).

This objection also applies to those independent claims using, employing and referring to the modulator of claim 19, *i.e.* claims 21-23, 25 and 26 (See the International Search Report).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

-

Reference is made to the following document:

D1: EP-A-0 605 797 (BEHRINGWERKE AG) 13 July 1994 (1994-07-13), cited in the application on page 2, line 33

-

1. Claims 1-11:

The application discloses a series of peptides (claims 1-6, 10) or variants thereof (claims 7-9) "capable of modulating a fibrin fragment E activity", which peptides or variants thereof can be fused to another peptide (claim 11).

The document **D1** is regarded as being the closest prior art to the subject-matter of claims 1 and 4, and shows (the references in parentheses applying to this document) fragment E fragments (page 3, lines 29-41), and the use of these fragments for therapy of fibrinolytic disorders (page 5, lines 7-8).

The subject-matter of claims 1 or 4 therefore **differs** from these known peptide fragments in that the peptides disclosed in claims 1 or 4 are different to the fragment E peptide fragments.

The subject-matter of **claims 1 or 4** is therefore **novel** (Article 33(2) PCT).

The **problem** to be solved by the present invention may therefore be regarded as to provide alternative peptide fragments, having a fibrin fragment E activity.

The **solution** to this problem proposed in **claims 1 or 4** of the present application is considered as involving an **inventive** step (Article 33(3) PCT), because none of the available prior art documents discloses or suggests a peptide as disclosed in claims 1 or 4.

Claims **2 and 3** are dependent on claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

Claims **5-9** are dependent on claim 4 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

Claims **10 and 11** are dependent on claims 1 or 4 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

2. Claims 12 and 27-29:

The application discloses as well nucleic acids encoding such peptides (claims 12

and 29), an expression vector comprising said nucleic acid (claim 27), and a host cell carrying said vector (claim 28).

As none of the available prior art documents discloses or suggests such nucleic acids, the subject-matter of **claims 12 and 27-29** is considered **new** and **inventive** (Article 33(2) and 33(3) PCT).

3. Claims 13-18, 20, and 24:

The application discloses an antibody capable of biding selectively to said peptides (claims 13-14); a method of identifying a peptide "capable of modulating a fibrin fragment E activity" comprising the steps of (1) providing an antibody according to claim 13, (2) contacting said antibody with the putative modulator compound, (3) determining if the antibody is able to bind the compound selectively (claims 15-17, 24); a process for producing said modulator compound (claim 18); and the use of the antibody of claim 13 for identifying the active site of fibrin fragment E receptor (claim 20).

The document **D1** is regarded as being the closest prior art to the subject-matter of claim 13, and shows (the references in parentheses applying to this document) fragment E fragments (page 3, lines 29-41), and the use of these fragments for raising antibodies against fragment E (claim 7). Said antibodies are used to monitor hyperfibrinolytical state (claims 19-20).

The subject-matter of claim 13 therefore **differs** from these known antibodies in that the antibodies disclosed in claim 13 are specific for the new and inventive peptides of claims 1-11.

The subject-matter of **claim 13**, and of its dependant claim **14**, can therefore be considered **new** (Article 33(2) PCT) and **inventive** (Article 33(3) PCT).

A method using the new and inventive antibody of claim 13 can be considered **n w** and **inventive**; therefore, the subject-matter of **claims 15-18**, **20** and **24** complies with the requirements of PCT Articles 33(2) and 33(3).

4. Industrial application:

The subject-matter of claims 1-11 have an **application** as modulators of mimics of fibrin fragment E.

Therefore, the subject-matter of **claims 1-18, 20, 24 and 27-29** complies with the requirements of PCT Article 33(4).

Re Item VIII

Certain observations on the international application

The use of the expression "*incorporated by reference*" (page 13, lines 3-4) is not allowed in some designated Contracting States.

CRAHSFVSPRPLPVV (SEQ ID NO:3)
QPDPHLMMWKLPGFP(SEQ ID NO:4)

or a fragment thereof capable of modulating fibrin fragment E activity.

As described above, fibrin fragment E activity refers to at least one of following activities: induction of cell proliferation, angiogenesis, fibrogenesis and collagen synthesis.

In a further aspect of the invention, there is provided a functional variant of the above peptide, which variant comprises from one to four, preferably from one to three, more preferably one or two, amino acid variations, including substitutions, insertions and deletions. Preferably, the variant retains the capability of modulating fibrin fragment E activity.

In another aspect of the invention there is provided a fusion peptide which comprises a first portion having the amino acid sequence of a peptide according to the invention as defined above and a second portion, attached to the N- or C- terminus of the first portion, which comprises a sequence of amino acids not naturally contiguous to the first portion. Such heterologous peptide fusions are also referred to herein as peptides of the invention.

In a further aspect, the invention provides assay methods for the identification of substances which bind to or modulate the activity of peptides of the invention, either in monomeric or oligomeric form.

In a further aspect of the invention, "analogs" of the peptides of the invention are provided. Analogs are non-peptide compounds which share fibrin fragment E activity, for example the ability to competitively inhibit binding of FDPs ,

carbonyl linkages, leading to a branched structure which may in turn be branched one or more times. By way of example, four copies of a peptide of the invention may be joined to such a multiple antigen peptide (MAP), such as a MAP of the structure Pep_4-Lys_2-Lys-X, where Pep is a peptide of the invention (optionally in the form of a heterologous fusion), Lys is lysine and X is a terminal group such as β-alanine which provides for joining of the MAP core to a solid support such as a resin for synthesis of the Pep_4-MAP peptide and which may be removed from the support once synthesis is complete.

Linear multimers of peptides of the invention may also be provided.

Other multiple peptide structures may be obtained using the MAP cores described in: Lu *et al*, 1991, Mol Immunol, 28, 623-30; Briand *et al*, 1992, J Immunol Methods, 156, 255-65; Ahlborg, 1995, J Immunol Methods, 179, 269-75.

A multimer of peptides of the present invention may be fused to a translocation peptide for directing it through the membrane of a eukaryotic cell, as discussed herein. A translocation peptide may be fused to an N-terminus or a C-terminus of the multimer, or it may be incorporated at an intermediate position within the multimer.

Where multimers of the invention are provided, they may comprise different peptides of the invention or be multimers of the same peptide.

Production and Modification of Peptides.

Except where specified to the contrary, the peptide sequences described herein are shown in the conventional 1-letter code and in the - terminal to C-terminal orientation. The amino acid sequence of peptides of the invention may also be modified to include non-naturally-occurring amino acids or to

side chains where desired using chemistry known per se in the art.

Expression Vectors, Nucleic Acids and Host Cells

In another aspect, the invention provides nucleic acids encoding peptides of the invention. Polynucleotides of the invention can be incorporated into a recombinant replicable vector. The vector may be used to replicate the nucleic acid in a compatible host cell. Thus in a further embodiment, the invention provides a method of making polynucleotides of the invention by introducing a polynucleotide of the invention into a replicable vector, introducing the vector into a compatible host cell, and growing the host cell under conditions which bring about replication of the vector. The vector may be recovered from the host cell. Suitable host cells are described below in connection with expression vectors.

Preferably, a polynucleotide of the invention in a vector is operably linked to a control sequence which is capable of providing for the expression of the coding sequence by the host cell, i.e. the vector is an expression vector.

The term "operably linked" refers to a juxtaposition wherein the components described are in a relationship permitting them to function in their intended manner. A control sequence "operably linked" to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences.

Such vectors may be transformed into a suitable host cell to provide for expression of a peptide of the invention. Thus, in a further aspect the invention provides a process for preparing peptides according to the invention which comprises cultivating a host cell transformed or transfected with an expression vector as described above under conditions to

CLAIMS

1. A peptide selected from the group:
CRAHSFGSPRPLPVV (SEQ ID NO:1),
SRAHSFGSPRPLPVV (SEQ ID NO:2),
CRAHSFVSPRPLPVV (SEQ ID NO:3), and
QPDPHLMMWKLPGFP (SEQ ID NO:4);

or a fragment thereof capable of modulating a fibrin fragment E activity.

2. A variant peptide which is a variant of a peptide or fragment according to claim 1, which variant has from one, two, three or four amino acid substitutions, insertions or deletions with respect to said peptide or fragment wherein the variant peptide is capable of modulating a fibrin fragment E activity.

3. A peptide or fragment according to claim 1 or claim 2 wherein the said activity is stimulation of cell proliferation or angiogenesis.

4. A fusion peptide which comprises a first portion having the amino acid sequence of a peptide defined in any one of claims 1 to 3 and a second portion, attached to the N- or C-terminus of the first portion, which comprises a sequence of amino acids not naturally contiguous to the first portion, said second portion comprising a membrane translocation sequence.

5. An isolated nucleic acid encoding a peptide according to any one of claims the preceding claims.

6. An antibody or fragment thereof capable of selectively binding to a peptide according to any one of claims 1 to 4.

7. An antibody according to claim 6 which is a monoclonal antibody, a polyclonal antibody or antiserum.

8. A method of identifying a compound capable of modulating a fibrin fragment E activity, which compound is a peptide or an analog thereof, wherein said method comprises the steps of:
providing an antibody or binding fragment according to claim 6;
contacting said antibody or binding fragment with a putative modulator compound; and
determining whether said antibody or binding fragment is able to selectively bind to the compound.

9. A method according to claim 8 wherein the compound is provided in the form of an expression or chemical library.

10. The method according to claim 8 or claim 9 further comprising the step of testing the ability of the modulator to modulate fibrin fragment E induced cell proliferation and/or angiogenesis.

11. A process for producing a modulator comprising the step of identifying the modulator according to the method of any one of claims 8, 9 or 10.

12. A modulator of fibrin fragment E activity identified by the method according to any one of claims 8, 9 or 10.

13. Use of an antibody or binding fragment according to claim 6 in a method of identifying the active site of the fibrin fragment E receptor.

14. A composition comprising a peptide or fragment thereof according to any one of claims 1 to 4 or a modulator of claim 12 in association with a pharmaceutically acceptable

carrier or diluent.

15. A coronary stent comprising a peptide or fragment thereof according to any one of claims 1 to 4, a modulator of claim 12 or a composition according to claim 14.

16. A method of inhibiting stimulation of cell proliferation induced by a fibrin degradation product comprising bringing the cell into contact with a peptide according to any one of claims 1 to 4, a modulator of claim 12 , or a composition according to claim 14.

17. A method according to claim 8 wherein the said activity is stimulation of cell proliferation or angiogenesis.

18. A peptide according to any one of claims 1 to 4, a modulator of claim 12, or a composition according to claim 14 for use in a method of treatment of the human or animal body.

19. Use of a peptide according to any one of claims 1 to 4, a modulator of claim 12, or a composition according to claim 14 in the preparation of a medicament for the inhibition of cell proliferation

20. An expression vector comprising an isolated nucleic acid as defined in claim 5 operably linked to a promoter.

21 A host cell carrying a vector according to claim 19.

22. A nucleic acid primer consisting essentially of a sequence of between about 15 to 50 nucleotides encoding a peptide according to any one of claims 1 to 4.

INTERNATIONAL SEARCH REPORT

Inte .onal Application No
PCT/GB 00/02197

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K7/08 C07K16/44 C12N5/12 C12N15/11 C12N15/62
C12N15/63 G01N33/68 A61K38/10 A61P9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, STRAND, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 605 797 A (BEHRINGWERKE AG) 13 July 1994 (1994-07-13) page 5, line 6 - line 7; claims; examples ---	1
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1992 THOMPSON W D ET AL: "Angiogenic activity of fibrin degradation products is located in fibrin fragment E." Database accession no. PREV199395013436 XP002152690 abstract & JOURNAL OF PATHOLOGY, vol. 168, no. 1, 1992, pages 47-53, ISSN: 0022-3417 --- -/--	1,19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2000	28/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuhr, C

Form PCT/ISA/210 (second sheet) (July 1992)

Inter. .onal Application No
PCT/GB 00/02197

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1993 STIRK C M ET AL: "Presence of growth-stimulating fibrin degradation products containing fragment E in human atherosclerotic plaques." Database accession no. PREV199497070046 XP002152691 abstract & ATHEROSCLEROSIS, vol. 103, no. 2, 1993, pages 159-169, ISSN: 0021-9150 -----	1,6,19

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 12

Present claim 2 relates to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the compounds of claim 1 and fragments and variants thereof which have common structural features. Variants of fragments of the peptides of claim 1 are not covered by search because this would include compounds having no structural features common to those peptides of claim 1.

Present claim 12 relates to a product defined by reference to a desirable characteristic or property, namely being active in a identifcation process of claim 8.
The claims cover all products having this characteristic or property, whereas the application does not provide support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for claim 12.

The objections raised for the claims 2 and 12 also apply to dependent compound claims and to those independent claims using, employing and referring to the compounds mentioned above

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[illegible]onal Application No
PCT/GB 00/02197

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0605797 A	13-07-1994	DE 4242736 A	23-06-1994
		AT 177758 T	15-04-1999
		AU 676859 B	27-03-1997
		AU 5243593 A	30-06-1994
		CA 2111645 A	18-06-1994
		DE 59309458 D	22-04-1999
		ES 2129487 T	16-06-1999
		JP 6256388 A	13-09-1994
		US 5599678 A	04-02-1997
		US 5981697 A	09-11-1999